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Psoriasis Phenotype at Disease Onset: Clinical Characterization of 400 Adult Cases

Lotus Mallbris,* Per Larsson,† Susanne Bergqvist,* Eva Vingård,‡ Fredrik Granath,§ and Mona Ståhle*

*Dermatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; †Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; ‡Section of Personal Injury Prevention, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; §Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Psoriasis is clinically a heterogeneous disease. Detailed evaluation of phenotype at disease onset is lacking. This study is a baseline characterization of 400 adult individuals with first time incidence of psoriasis on non-hairy skin, describing clinical phenotypes and putative environmental triggers at disease onset. In total, 74 patients with guttate and 326 patients with non-guttate phenotype, the majority with plaque psoriasis, were included. Guttate phenotype was associated with younger age and recent infection in 84%, where acute streptococcal pharyngitis was verified in 63%. The predominating factor associated with onset of plaque psoriasis was a recent life crisis (46%). A positive family history for psoriasis was approximately the same in both groups. Psoriasis arthropathy was diagnosed in 5% of guttate and 15% of non-guttate patients, with enthesopathy being the dominant symptom among guttate patients. This study confirms the strong link between onset of guttate psoriasis phenotype and streptococcal throat infection, whereas onset of plaque psoriasis was highly associated with a preceding distinct stressful life event. Longitudinal follow-up of the patients will provide robust information about disease development and response to treatment.

Key words: guttate psoriasis/life change events/precipitating factors/psoriasis phenotype/streptococcal infection
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Psoriasis is a common, hereditary, and chronic inflammatory skin disorder affecting more than 2% of the Swedish population (Hellgren, 1967). The disease appears to be both genetically and clinically heterogeneous, and several phenotypes have been described. The age at onset ranges from early childhood to late adulthood. In a large epidemiological study in Sweden, three peaks for age at onset were found: at puberty, at the age of 30 y, and at the age of 50 y (Swanbeck *et al*, 1995).

Epidemiological circumstances surrounding disease debut and the pathogenetic mechanisms inducing the psoriasis skin phenotype are not clear. A host of environmental factors, however, have been incriminated in precipitating and worsening psoriasis; including streptococcal infection (Telfer *et al*, 1992; Rasmussen, 2000; Gudjonsson *et al*, 2003), cutaneous trauma (Eyre and Krueger, 1982), drugs (Abel *et al*, 1986; Tsankov *et al*, 1998), alcohol and cigarette smoking (Naldi *et al*, 1992; Higgins, 2000), stress (Seville, 1989; Naldi *et al*, 2001), and in a minority of patients, ultraviolet radiation (Ros and Eklund, 1987). Furthermore, among the various factors thought to be associated with psoriasis, a link to autoimmune disorders, such as celiac disease, vitiligo, and autoimmune thyroid disease, has been reported. In fact, a high prevalence of celiac disease has been shown in patients with psoriasis (Ojetti *et al*, 2003).

The natural history of psoriasis has been thoroughly studied retrospectively in various psoriasis populations. The purpose of this study was to establish detailed baseline characterization of adult psoriasis patients at disease onset. The study design allows high specificity and reliable assessment of clinical features, triggering factors, and age of onset. Since ethical permission to include children was not obtained at the time, this study comprises only individuals above 15 y of age.

Results

Distribution of sex and age The age at onset ranged from 15 to 84 y, with a mean age of 41 (median age of 40 y). Overall, the proportion of patients was approximately equal in the early and late onset groups ($n = 204$ early onset *vs* $n = 196$ late onset). The age patterns in the different phenotypes demonstrated a single distinct peak and an earlier onset in the guttate phenotype, whereas the age at onset occurred later among patients with non-guttate phenotype. The sex distribution showed a slightly higher female proportion, 56%.

Phenotypes The Relative frequencies of phenotypes are shown in (Table I). In total, 400 patients were included in the study. The largest group, regardless of age, was non-guttate psoriasis (81%, $n = 326$). In addition to plaque psoriasis,

Abbreviations: AGA, serum IgA antibody to gliadin; BMI, body mass index; EmA, IgA antibodies to endomysium; PASI, psoriasis area severity index; PGA, physician's global assessment; RF, rheumatoid factors; TgA, IgA anti-transglutaminase

Table I. Clinical characterization of psoriasis phenotype at onset in relation to environmental factor

	Guttate (%)		Non-guttate (%)		
	⩽40 (n = 58)	>40 (n = 16)	⩽40 (n = 146)	>40 (n = 180)	Total (%) (n = 400)
Sex					
Female	52	62	51	61	56
Clinical examination					
Skin					
Phenotype	78	22	45	55	
Combined with[a]					
+ face	21	19	23	9	17
+ nail	3	—	8	19	12
+ Köbner phenomenon	19	6	3	2	5
Joints					
Arthritis[a]	5	6	15	17	14
DIP predominant	—	—	—	1	
Symmetric oligoarthritis	—	—	1	2	
Asymmetric polyarthritis	4	6	11	14	
Spondylitis	4	—	7	8	
Peripheral enthesopathy[b]	2	12	3	8	5
Precipitating factors					
Unknown	4	6	37	39	32
Only life crisis[c]	12	13	44	48	40
Only infections[d]	57	62	11	8	18
Infection + life crisis	27	19	8	5	10

[a]Not mutually exclusive, why it adds up to >100%.
[b]Without arthritis.
[c]Severe event profoundly affecting life with 2 mo prior to psoriasis onset, without ongoing infections.
[d]Without life crisis.
DIP, distal interphalangeal.

the non-guttate group included palmo-plantar (n = 7), inverse (n = 5), erythrodermic (n = 1), pustular (n = 1), acropustulosis (n = 1), and seborrhoeic (n = 1) psoriasis. But, the small number of these phenotypes did not allow separate analyses. Among patients with onset of plaque psoriasis, five individuals (four females and one male) had concurrent pustulosis palmoplantar psoriasis.

Seventy-four individuals, 18%, had a guttate phenotype at disease onset. Guttate psoriasis was more frequently observed in patients with early onset (78%, n = 45), whereas patients with a non-guttate phenotype were approximately equally distributed in the two age groups (45% early *vs* 55% late onset). In this material, patients with guttate phenotype were significantly younger than those with non-guttate phenotype ($p < 0.001$).

Facial involvement occurred in 17% of patients (n = 66) and was slightly more common among guttate patients (20% guttate *vs* 16% of non-guttate patients). Among non-guttate patients, facial lesions occurred more often in younger individuals, whereas there was no difference between age groups in patients with guttate phenotype.

The Köbner phenomenon was observed in 5% of all patients (n = 20), of whom more than half (n = 11) had early onset of guttate phenotype, probably indicating a more eruptive and active form of onset.

Forty percent of patients (n = 158) reported pruritus associated with psoriasis, occurring equally among groups.

Psoriasis area severity index (PASI) and physician's global assessment (PGA) We used PASI and PGA methods in parallel to assess the severity of cutaneous involvement. We observed a high level of concordance for the two methods. The average time span from disease onset to skin examination was 4 mo for guttate patients and 7 mo for non-guttate patients. Most patients were without active treatment at the time of examination. But, less than 4% of patients (n = 14), with equal sex distribution, had received systemic treatment before examination. A minority of patients (4%, n = 14) were in remission at the time of entry. In these patients, the diagnosis was secured from medical records and patients were followed up at our clinic to ascertain the diagnosis. Overall, approximately 60% of the patients were evaluated as having mild disease, whereas more than one-third had moderate and only 3%–5% had severe psoriasis at examination.

Nail involvement Finger nail involvement was detected in 12% of patients (n = 47), the majority, 96% (n = 45), being of the non-guttate phenotype. Nail changes were also more frequent in patients with late-onset psoriasis (17% late *vs* early onset 6%, $p < 0.001$). There was no significant correlation between nail involvement and psoriasis arthropathy or PASI score in this study. Most nail changes were estimated as mild. But, 1% (n = 5) had severe nail involvement, all of whom were of non-guttate phenotype with late onset.

Psoriasis arthropathy Overall, 14% of patients (n = 54) had psoriasis arthritis with or without enthesopathy at disease onset. Five percent of patients (n = 21) had only enthesopathy without arthritis (Table I). The majority of patients with arthritis were found among the non-guttate patients, whereas enthesopathy was equally common among patients with guttate psoriasis (Table I).

Associated environmental factors The relative frequency of potential disease triggers is shown in (Table I). In total, 113 patients (28%) had a positive history of infection (with or without life crisis) preceding psoriasis onset. The most frequent infection was streptococcal pharyngitis, which was the most common precipitating factor for patients with guttate phenotype. Overall, 84% of patients with guttate psoriasis (n = 62) had a history of infection (with or without life crisis) prior to occurrence of skin lesions, and the majority of these patients (n = 46) had a verified streptococcal pharyngitis. Only 7% of patients (n = 23) with non-guttate phenotype had verified streptococcal pharyngitis. Thus, streptococcal pharyngitis was almost nine times more common in patients with guttate than in non-guttate psoriasis ($p < 0.001$).

The most common precipitating factor for patients in the non-guttate category, without streptococcal pharyngitis, was a life crisis within 2 mo prior to disease onset.

Family history of psoriasis Overall, complete information about family history was available in 378 patients (95%). Of the 22 individuals who lacked information, four were adopted and 18 lacked information about the complete family, usually missing information about one parent (Table II).

Among individuals in whom information was available, 52% reported a positive family history of psoriasis, including first-, second-, and third-degree relative/s. Thirty-four percent (126/378) indicated the presence of psoriasis in at least one first-degree relative. The minimum estimate for the cases was 32% for a positive family history in a first-degree relative, if all cases were considered in the denominator (126/400). Positive family history in a first-degree relative was approximately the same for guttate, 30% (n = 22) and non-guttate, 35% (n = 127) individuals. Among patients with psoriatic arthropathy, irrespective of skin phenotype, 27% (20/75) had a first-degree relative with psoriasis. Thus, in our study, positive family history was comparable among different clinical phenotypes at onset and did not affect the expression of psoriasis arthropathy.

Co-morbidity A summary of concomitant diseases in the study population is presented in Table S1. No patient had ongoing atopic eczema, but a history of previous flexural dermatitis in childhood was present in all groups and was most pronounced in young patients with a guttate phenotype. Other atopic manifestations were present in all groups.

As expected, cardiovascular diseases, in particular hypertension, were mostly found among older patients. Increased body mass index (BMI) was observed in 30% and obesity in 13% of patients.

The prevalence of celiac disease was approximately 1% in patients. Biopsy from the small intestine verified celiac disease in four of the patients.

Laboratory analyses Total serum IgA was elevated in 12% of guttate patients (n = 9) compared with 8% of non-guttate patients (n = 25). The proportion of patients who had increased serum IgA levels did not differ between patients with or without arthritis.

Serum levels of serum IgA antibody to gliadin (AGA) did not differ between phenotypes, but there was a gender difference, with 6% of the women being positive and only 3% of the men.

Overall, IgM rheumatoid factor (RF) was elevated in eight patients (2%). The highest prevalence of RF was found among older patients with a non-guttate phenotype (seven individuals) and of these, three were previously diagnosed with rheumatoid arthritis, one patient had psoriasis erythrodermia with psoriasis arthritis, and the remaining three had no joint problems. Among guttate patients, only one had positive RF and this patient had no joint complaint and was below 40 y of age.

Discussion

This study represents a unique effort to characterize adult psoriasis patients with regard to phenotype and precipitating factors at the onset of disease.

To reduce problems of generalization, patients were recruited through multiple channels, including self-referral. Despite these efforts, one may question whether the patients are representative for psoriatic patients in general. It is likely that patients with a high degree of concern and with a more acute onset of disease, especially when associated with an infection, might be more prone to seek health care than patients with a more insidious onset. This may explain

Table II. Family history of psoriasis

	Guttate (%)		Non-guttate (%)		
	⩽40 (n = 57)	>40 (n = 16)	⩽40 (n = 138)	>40 (n = 167)	Total (%) (n = 400)
First-degree relative/s	32	25	38	31	34
Second and third-degree relative/s	18	19	22	16	18

the relatively high proportion of patients with a guttate phenotype in this study, 19%, compared with 14% reported previously in adult psoriasis in Sweden (Molin, 1973). Then again, according to the study design, we have included patients consecutively without any restrictions concerning disease severity, whereas the previous study included only patients who required hospitalization because of their psoriasis. Also, the female dominance (approaching 1.3:1) in this study may reflect sex-related preference in seeking health care (Health and Medical Care 1980–2000, 2002), whereas, previous reports have observed either an equal sex distribution or a male predominance among patients with psoriasis.

Likewise, prior knowledge about psoriasis and presence of psoriasis in the family, and campaigns on the website and magazine of the Swedish Psoriasis Association may influence the inclination to seek medical advice at an early stage and render individuals who are familiar with psoriasis more willing to participate. This may explain why we record a higher familial occurrence of psoriasis among patients with late onset compared with previous studies (Henseler and Christophers, 1985; Ferrandiz *et al*, 2002). A detailed analysis of the familial tendency to develop psoriasis is not the focus of this study and thus, we do not account for differences in family size and number of affected family members.

Our results indicate that the dominant precipitating factor for non-guttate phenotype is a recent distinct life crisis. The association between onset and exacerbation of psoriasis with stress is much debated and previous studies point in different directions. A recent study comprising 40 patients with mixed psoriasis phenotypes showed no evidence for an influence of stressful life events on psoriasis symptoms (Picardi *et al*, 2003), whereas other studies suggest a link between psycho-social stress and both onset and exacerbation of psoriasis (Naldi *et al*, 2001; Fortune *et al*, 2003). Obviously, more epidemiological and experimental research is needed to understand this potentially key issue in expression of psoriasis phenotype. In this study, clinical examination and evaluation of patient history occurred in association with disease debut, which is likely to substantially increase the reliability of information and thus support the relationship between a life crisis and the expression of plaque psoriasis lesions.

In patients with guttate psoriasis, we confirm and strengthen the solid link between streptococcal pharyngitis and guttate onset (Telfer *et al*, 1992; Leung *et al*, 1995; Valdimarsson *et al*, 1995). We must acknowledge, however, that the time lead between onset of skin symptoms and clinical examination was shorter in guttate patients, which may partly influence the identification of streptococcal infection.

Among patients with a guttate phenotype, three patients presented with cutaneous infection, where we confirmed the presence of streptococcus pyogenes in the skin but not in the throat. Evidently, the association between psoriasis onset and streptococci is not confined to mucosal involvement, even though it is by far the most common location.

Nail involvement was more common among patients with non-guttate phenotype and was 2.5 times more frequent in the older age group compared with the group with early onset. These findings seemingly disagree with earlier studies, which indicate a positive correlation between nail psoriasis and early onset of disease (Ferrandiz *et al*, 2002; Stuart *et al*, 2002). These reports, however, describe psoriasis patients with highly variable disease duration and the results may reflect the positive association between nail psoriasis and duration of skin lesions as has previously been suggested (de Jong *et al*, 1996).

Psoriasis arthritis was diagnosed in 13.5% ($n = 54$) of all patients and was more common among patients with a non-guttate phenotype in accordance with previous reports (Ferrandiz *et al*, 2002). The standardized clinical examination of all patients reporting any degree of joint complaints may have precipitated the diagnosis of psoriasis arthropathy in patients with mild disease not spontaneously seeking rheumatologic care, thus maximizing the association. Enthesopathy without manifest arthritis was diagnosed in 5% of all patients and was also found among young patients with guttate psoriasis. Follow-up of these patients is required to assess to which extent the enthesopathy reflects an acute self-limiting reaction or will develop into manifest arthritis and to which extent the joint symptoms will parallel the skin disease.

Information about co-morbidity at onset of psoriasis is lacking. Multiple studies indicate a low prevalence of atopic eczema in psoriasis patients (Christophers and Henseler, 1987; Henseler and Christophers, 1995). Our present data, however, indicate that a history of childhood atopic eczema is not uncommon among patients with a guttate phenotype. Guttate psoriasis represents a more volatile eczematous inflammatory reaction than plaque psoriasis and one could speculate whether patients who present with guttate psoriasis may be inherently prone to developing acute inflammatory skin responses. Interestingly, recent genetic data point to partially overlapping candidate loci between psoriasis and atopic eczema, which may suggest shared underlying pathomechanisms (Speckman *et al*, 2003; Bowcock and Cookson, 2004).

Increased cardiovascular morbidity is reported in psoriasis and epidemiological data suggest that the risk for cardiovascular disease is more pronounced in severe psoriasis (Henseler and Christophers, 1995; Poikolainen *et al*, 1999; Mallbris *et al*, 2004). As expected, the prevalence of cardiovascular disease in this study was mostly confined to the older age group. Previous studies suggest that one established risk factor for cardiovascular disease, namely an elevated BMI, is higher in patients than in the control population controls, underlining the potential metabolic aspect of psoriasis (Lindegard, 1986; Henseler and Christophers, 1995). Whether the diagnosis of psoriasis will produce divergent development in BMI over time will be an interesting issue to be followed.

Increased levels of autoantibodies toward gliadin have previously been demonstrated in psoriasis and psoriasis arthritis (Michaelsson *et al*, 2000; Lindqvist *et al*, 2002; Ojetti *et al*, 2003). In this study, we detected higher levels of AGA among patients with late onset. Since previous studies report on patients with highly variable disease duration, it will be interesting to see whether significant differences will emerge and if so whether they are associated with distinctive phenotypic traits.

This study represents the initial baseline description of adult psoriasis patients examined within 1 y after onset of

skin lesions. The sample size is not sufficient to detect association with rare disorders at this point. But, additional patients are being recruited along with population-matched controls and the first follow-up of patients, at 4 y after onset, is being initiated. Thus, these patients form the basis for a biobank allowing for genetic and molecular studies and longitudinal follow-up, which will create robust knowledge about psoriasis development, associated co-morbidities, and potential epidemiological links.

Material and Methods

Patients Patients above 15 y of age with onset of psoriasis lesions on non-hairy skin within the past 12 mo were eligible to enter the study. Patients were seen consecutively by two dermatologists (L. M., M. S.), at the department of Dermatology, Karolinska Hospital, Stockholm, Sweden, between 2001 and 2003. Individuals with a previous diagnosis or a history of skin lesions compatible with psoriasis were excluded. Patients were classified into two subgroups: onset $\leqslant 40$ y, early onset, and onset >40 y, late onset.

The study consists of 400 patients, 175 males and 225 females, mainly originating from Sweden and mostly recruited from the Stockholm area through the advertisements in two different free-distributed daily newspapers, campaigns on the website and magazine of the Swedish Psoriasis Association, referrals from private dermatologists, other dermatology clinics, general practitioners, school nurses, sexual health centers, and youth clinics.

In total, 950 individuals either responded or were referred. Prior to clinical examination, a telephone interview was conducted by the examining physician or an experienced nurse trained in psoriasis. Four hundred and twenty individuals were examined clinically, of which 400 were eligible to enter the study. Only subjects with a clinically convincing diagnosis of psoriasis were included.

Patients were classified according to the pattern and severity of psoriasis lesions on skin, presence or absence of nail involvement, and psoriasis arthropathy at the time of initial examination. All individuals with any joint symptoms were examined by an experienced rheumatologist (P. L.).

Additional information included a family history of psoriasis, history of recent infections, stressful events within 2 mo prior to onset, and other potentially predisposing factors surrounding onset and previous and ongoing medication. Written informed consent was given by all patients. The study was approved by the Regional Committee of Ethics. The study was performed according to the Declaration of Helsinki Principles.

Participation Participation involved attending a clinical examination, answering a questionnaire, and providing blood samples for laboratory analyses.

Skin examination Diagnosis and classification of psoriasis were made using established terminology (Christophers and Sterry, 1993). Guttate psoriasis was defined as acute onset of scattered small coin-like lesions. Non-guttate psoriasis included nummular and large plaque type. Single patients with other distinct phenotypes were also recruited.

Measurement of skin disease severity was performed using both PASI and PGA in parallel. A PASI score below 3 was defined as mild, between 3 and 15 as moderate, and above 15 as severe disease.

All medical records for subjects (3.5%, $n=14$) who had received psoriasis diagnosis and treatment leading to remission prior to inclusion were requested and evaluated.

Nail examination Both fingernails and toenails were examined clinically. But, only assessment of fingernails was taken into account, since clinical evaluation of toenails may be complicated by frequent fungal infections.

Each nail was evaluated separately and was assigned a severity score depending on disease activity (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The sum of the total score from all nails gave a total score ranging between 0 and 30. The interval 0–10 was classified as mild nail involvement, 11–20 moderate, and 21–30 severe.

The evaluation included pitting, defined as a minimum total of two pits on a nail, onycholysis, leukonychia, hyperkeratosis, oil drops, and crumbling.

Joint examination Patients with joint symptoms were subdivided into five groups (Moll and Wright, 1973): patients with (1) arthritis in distal interphalangeal joints, (2) symmetric polyarthritis, (3) asymmetric mono-oligoarthritis, (4) spondylitis, and (5) peripheral enthesopaty without arthritis. All joint evaluations were performed by the same rheumatologist.

Associated environmental factors Associated and potentially inducing environmental factors were recorded. Life crisis was defined as a distinct severe event profoundly affecting life occurring within 2 mo prior to disease onset, and in the absence of streptococcal pharyngitis. Life crisis included divorce, severe/life-threatening diseases affecting the patient or close family members, deaths within the close family, serious financial difficulties, being dismissed from work, and harassment at school. Infection was defined as acute symptoms requiring antibiotics or antiviral treatment (one case) occurring up to 10 d before onset of psoriasis.

Family history At inclusion, a family history was carefully obtained by the examining dermatologist. A diagnosis of psoriasis in any first- (biological parents, siblings and children), second- (biological grandparents, grandchildren, uncles, and aunts), or third- (biological first cousins) degree relative/s was recorded.

Laboratory analyses

IgA antibody to gliadin and RF AGA, reference <50 U per liter, total serum IgA (reference 07–4.5 g per liter), IgA antibodies to endomysium (EmA), IgA anti-transglutaminase (TgA), and IgM RF were measured in all patients, using routine laboratory methods. Seropositivity for IgM RF was defined as a Waaler–Rose titer of 40 or more (Husby *et al*, 1988).

All individuals ($n=5$) positive for EmA and/or TgA in serum underwent endoscopic evaluation including biopsies from the small intestine. Specimens were evaluated by a pathologist for severe to total villous atrophy, crypt hyperplasia, and lymphocyte infiltration to confirm celiac disease.

Streptococcal throat infection A throat-swab for culture as a diagnostic test for streptococcal infection was obtained from all patients.

BMI BMI was calculated for all patients. Increased BMI was defined as a BMI between 25 and 30 kg per m^2 and obesity as a BMI above 30 kg per m^2 (Bray, 1987).

Statistical analyses Comparison between guttate and non-guttate with respect to clinical manifestations, precipitating factors, family history, and co-morbidity was performed by Fisher's exact test.

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Supplementary Material

The following material is available from http://www.blackwellpublishing.com/products/journals/suppmat/JID/JID23611/JID23611sm.htm
Table S1. Co-morbidity in psoriasis at onset

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Address correspondence to: Mona Ståhle, Unit of Dermatology, Department of Medicine, Karolinska Institutet, 171 76 Stockholm, Sweden. Email: mona.stahle@medks.ki.se

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